

Autism and psychosis traits diametrically modulate the right temporo-parietal junction

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Abstract: The mentalizing network is atypically activated in autism and schizophrenia spectrum disorders. While these disorders are considered diagnostically independent, expressions of both can co-occur in the same individual. We examined the concurrent effect of autism traits and psychosis proneness on the activity of the mentalizing network in 24 neurotypical adults while performing a social competitive game. Activations were observed in the paracingulate cortex and the right temporo-parietal junction (rTPJ). Autism traits and psychosis proneness did not modulate activity within the paracingulate or the dorsal component of the rTPJ. However, diametric modulations of autism traits and psychosis proneness were observed in the posterior (rvpTPJ) and anterior (rvaTPJ) subdivisions of the ventral rTPJ, which respectively constitute core regions within the mentalizing and attention-reorienting networks. Within the rvpTPJ, increasing autism tendencies decreased activity, and increasing psychosis proneness increased activity. This effect was reversed within the rvaTPJ. We suggest that this results from an interaction between regions responsible for higher level social cognitive processing (rvpTPJ) and regions responsible for domain-general attentional mechanism (rvaTPJ). The observed diametric modulation of autism tendencies and psychosis proneness of neuronal activity within the mentalizing network highlights the importance of assessing both autism and psychosis expressions within the individual.

Keywords: Attention-reorienting; Diametric Model; fMRI; Mentalizing; Schizophrenia; TPJ

Introduction

Difficulty with inferring the mental states of others (“mentalizing” or “Theory of mind”) is a core feature of both Autism Spectrum Disorders (ASD) and Schizophrenia Spectrum Disorders (SSD) (Chung et al 2013). Research concerned with understanding the neural system of mentalizing has identified a network of regions that primarily involves the temporo-parietal junction (TPJ) and the medial prefrontal/paracingulate cortex (Abu-Akel & Shamay-Tsoory 2011, Saxe & Kanwisher 2003). Atypical alterations in this network have been observed independently in

individuals with ASD (Ciaramidaro et al 2015, Kana et al 2009, Lombardo et al 2011) and SSD (Ciaramidaro et al 2015, Walter et al 2009). These atypicalities have also been observed as a function of subclinical expressions of autism (Nummenmaa et al 2012, von dem Hagen et al 2011) and psychosis (Modinos et al 2010, van der Meer et al 2013) within the healthy population.

These findings are often interpreted as support for the view positing that ASD and SSD and their extended spectra are overlapping conditions (Dinsdale et al 2013, King & Lord 2011, Solomon et al 2011), with multiple phenotypic similarities and risk factors (Carroll & Owen 2009, Chisholm et al 2015, Hamlyn et al 2013). This raises important questions about the nature of the relationship of these phenotypes within an individual. An alternative to the model of overlap between ASD and SSD, the diametric model (Abu-Akel & Bailey 2000, Crespi & Badcock 2008) conceptualizes ASD and SSD as opposite diametric conditions, such that their constituent traits should specifically not overlap to any large degree. Central to this model is that deficits in both disorders would deviate in opposite directions from typicality. Thus, in considering functionality within the mentalizing network, the overlapping model would predict that both ASD and SSD would affect its neural activity in the same manner, whereas the diametric model would predict that ASD and SSD would exert effects in opposite directions.

One approach to evaluating these two competing hypotheses, i.e., regarding the effect of ASD and SSD on the neural activity of the mentalizing network, is to examine its activity as a function of the expression of autistic tendencies and psychosis proneness within non-clinical

populations. This approach draws on the notion that autism tendencies and psychosis proneness are dimensions of normal variation (Baron-Cohen et al 2001, Crespi et al 2010, Del Giudice et al 2014, Dinsdale et al 2013, Nettle 2006), with the clinical entities being at the extreme of this distribution. This approach also eliminates the confounding effects of medication, chronicity or active symptomatology (Ettinger et al 2015, Stefansson et al 2014). Our approach thus ensures that the observed effects and performance are not due to severe alteration in brain activity and structure often associated with these confounds. To this end, we performed a functional magnetic resonance imaging study in 24 right-handed neurotypical adults while playing the well-known playground game of Rock, Paper, Scissors (RPS) (see Method). This task has been shown to reliably activate the mentalizing network in a competitive context (Chaminade et al 2012, Gallagher et al 2002) and specifically the rTPJ and the medial prefrontal/paracingulate cortex. We thus asked whether variation in the co-occurrence of autism tendencies and psychosis proneness has an impact on the neural activity of these core regions within the mentalizing network of neurotypical brains.

Previous mentalizing studies suggested that ASD and SSD are variably associated with hypo- and hyper-activation within the mentalizing network. For example, studies showed that delusional symptoms in SSD patients (Backasch et al 2013) were associated with increased activations in the posterior superior temporal sulcus (TPJ adjacent) and the medial prefrontal cortex (MPFC). A more recent study showed that positive symptoms of paranoid schizophrenia patients (Ciaramidaro et al 2015) were associated with increased activation in the MPFC in conditions where the attribution of intentionality was not warranted (e.g., physical conditions).

In the same study, reduced activation in the dorsal MPFC was associated with *hypo-intentionality* in the ASD group, whereas increased activations were associated with *hyper-intentionality* in the paranoid schizophrenia group. In addition, Lombardo and colleagues (Lombardo et al 2011) reported that the activity of the rTPJ in ASD participants was reduced compared to healthy controls, and predicted their social impairment (see also (Kana et al 2015)). Furthermore, a meta-analysis of theory of mind studies in ASD and SSD, revealed hypo-activation of the TPJ in ASD, and hypo-activation of the MPFC in both ASD and SSD, relative to healthy controls (Sugranyes et al 2011). Intriguingly, a direct comparison between the ASD and SSD revealed that (i) MPFC hypo-activation was more pronounced in ASD, (ii) somatosensory regions were more active in SSD, and (iii) the insula was more active in ASD. Taken together, we predict that autism tendencies and psychosis proneness would have contrasting effects on TPJ and MPFC activity, such that activity would be negatively associated with autism tendencies and positively associated with psychosis proneness.

However, the precise role of the rTPJ within the mentalizing network has been the subject of competing hypotheses from both the functional and ‘territorial’ perspectives. Functionally, the rTPJ, in addition to its role in mentalizing, has been implicated in saliency, attention-reorienting and self-other distinction (Corbetta et al 2008, Decety & Lamm 2007). With respect to its territorial integrity, it is not clear whether the rTPJ is a shared neural region for all of these functions, or whether it consists of subregions supporting specific functions (Carter & Huettel 2013, Corbetta et al 2008, Decety & Lamm 2007, Mars et al 2012). In this regard, Mars and colleagues (Mars et al 2012), using diffusion-weighted imaging tractography-based

parcellation, have shown that the rTPJ consists of at least 3 subregions with distinct pattern of functional connectivity. These subregions consist of a dorsal subregion (rdTPJ), largely corresponding to the inferior parietal lobule, and a ventral subregion, which is further subdivided into posterior (rvpTPJ) and anterior (rvaTPJ) subregions (see Results, Figure 4). The rdTPJ is functionally connected with a network including the lateral anterior PFC and forms part of the Task Positive Network. The rvpTPJ and the rvaTPJ are respectively functionally connected with the mentalizing and the attention-reorienting networks. The association of the rvpTPJ and the rvaTPJ with mentalizing and attention-reorienting is consistent with a meta-analysis of 70 functional neuroimaging studies showing that, on average, attention-reorienting activates anteriorly and mentalizing processes posteriorly (Decety & Lamm 2007) (see also (Bzdok et al 2013, Schurz et al 2014)). Therefore, as a secondary aim, the current study investigated whether variation in the co-occurrence of autism tendencies and psychosis proneness has a specific impact on the neural activity of these subdivisions of the rTPJ.

Methods

Participants: 24 right-handed, English proficient healthy adults (5 Males; 19 Females; Mean Age \pm SD = 21.21 \pm 4.21) participated in the study. Participants did not have a history of psychiatric illness, epilepsy, neurological disorders, brain injury as well as current alcohol or substance abuse problems. The Research Ethics Committee of the University of Birmingham approved the study, and written informed consent was obtained from all participants.

Materials and procedures: Psychosis proneness, assessed using the positive scale of the Community Assessment of Psychic Experiences (CAPEp) Questionnaire (Stefanis et al 2002), autism tendencies, assessed using the Autism Spectrum Quotient (AQ) Questionnaire (Baron-Cohen et al 2001), English reading proficiency, assessed with the Test of Irregular Word Reading Efficiency (TIWRE) (Reynolds & Kamphaus 2007) and the Test of Word Reading Efficiency (TOWRE) (Torgesen et al 1999) questionnaires, and handedness, ascertained with the modified Annett Handedness Questionnaire (Annett 1972), were administered to 27 participants, on average 7-10 days prior to the scanning session. Of the 27 participants, 24 were scheduled for the scanning session during which they performed two tasks. Three participants could not attend the scanning session due to scheduling conflicts. The first task is a computerized version of the Rock, Paper, Scissors game. The second task is Hartwright et al.'s (Hartwright et al 2012) anglicized variant of Saxe and Kanwisher's (Saxe & Kanwisher 2003) theory of mind (ToM) functional localizer task. At the end of the scanning session, all participants went through a debriefing interview.

The theory of mind (ToM) localizer task. This task was used to reliably identify regions within the mentalizing network, which include the TPJ, the paracingulate/medial prefrontal cortex and precuneus and the temporal pole. In this task, participants read 24 short vignettes that were displayed on the screen for 10 seconds. Half of the stories described the false belief of a character about the current state of affairs (i.e., the False Belief (FB) stories), and the other half described a physical event that is non-concurrent with reality such as a photo of a past event (i.e., the False Photograph (FP) stories). Each story was followed by a true-false question that

was displayed for 4 seconds, and to which they responded using a response box with two active buttons that was placed in the participant's right hand. The task consisted of four short fMRI runs. In each run, six stories, 3 FB and 3 FP, were presented in an alternating order, interleaved with a 12.5sec rest period. All participants went through a practice session of four trials outside the scanner. The task was presented using Presentation (Neurobehavioural Systems, CA), which also recorded the behavioral data (response selection and reaction time).

The rock, paper, scissors (RPS) task. In this task, participants are required to predict the moves of their opponent in order to win. The game has the following simple rules: Rock beats scissors, paper beats rock, and scissors beat paper. The winner of each round is awarded 1 point. A no-response results in an automatic win for the opponent, and identical moves results in a draw and no points are awarded. Here, we orthogonally manipulated the intentional stance during the game in such a way that the participants are led to believe that they are playing under four conditions: (1) against an *active* human agent who is a skilled RPS player, (2) a *passive* human agent who is followed a predetermined script, (3) an *active* intelligent computer program (called AIRPS) that was capable of analyzing the participant's strategy, and (4) a *passive* computer program that followed a predetermined response script. These four conditions thus comprised a 2x2 experimental design with one factor being the human vs. computer opponent and the other factor being the element of implied agency from the opponent (active vs. passive).

Participants were cautioned not to use a stereotyped strategy and to play competitively with the intention of beating their opponent. Feedback was provided during the scan sessions as to how well the participant was scoring at the end of each block of ten rounds of the game and a summary of the results at the end of each fMRI run. Positive scoring and effort were rewarded with a prize of £10 for the highest performing participant overall at the end of the study. Before each one of the four conditions, participants were provided with on-screen instructions to remind them of what they are required to do and of the opponent against whom they would be playing. To reinforce the impression that the participant was truly playing against a 'human' opponent, a 3% fallibility 'no-response' measure was embedded during the human conditions.

Crucially, unbeknownst to the participants, the game was always played against a computer program generating moves entirely at random. The design ensured that the only difference across the conditions was the perceived identity of the participant's opponent under the various conditions. To check participants' perception of their opponents, a debriefing procedure was utilized after the scanning session during which participants were asked to recount how they understood and experienced these conditions. None of the participants expressed doubt regarding the identity of the four opponents.

The RPS experiment consisted of 5 fMRI runs, each lasting 440s per run (~40mins total). Each fMRI run consisted of 4 blocks, representing the four conditions of interest. The sequence of opponents was chosen from 8 predetermined player-sequences (chosen from the 24 possible sequences) such that on each sequence the human and the computer opponents were

presented in alternating order. The sequences the participants' played, in each of the 5 fMRI runs, were selected in a pseudorandom order.

Each block was preceded by a 10s period during which the instructions were displayed, and followed by a 30s rest period. During each block the participant played 10 trials against one of the four possible opponents. Response selections (i.e., rock, paper or scissors) were made using a button box with three active buttons that was placed in the participant's right hand. See Figure 1 for a schematic representation of stimuli presentation and timing during each trial. All participants went through a practice session of 2 blocks outside the scanner. The experiment was presented using Presentation (Neurobehavioral Systems, CA), which also recorded the behavioral data (button pressed and reaction time).

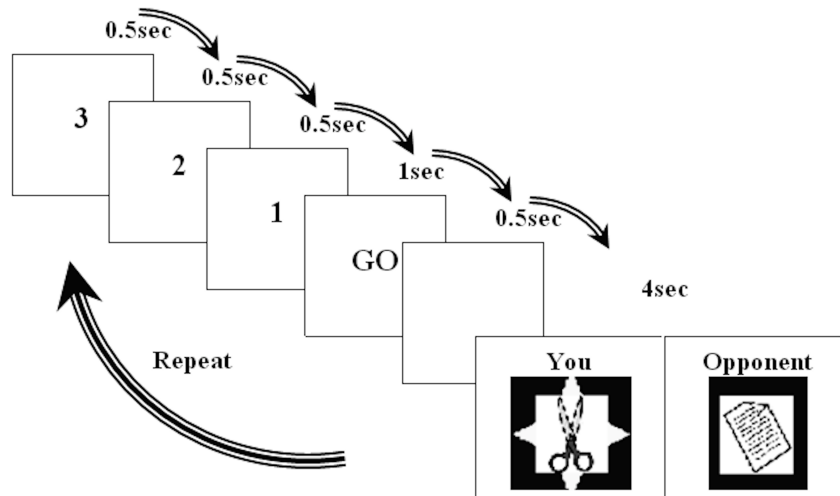


Figure 1. Each trial began with a countdown 3, 2, 1, in 0.5s intervals, followed by 'GO' during which the participants make their moves. The 'GO' was present for 1s followed by a 0.5s blank screen. The results screen is then displayed for 4s indicating the moves drawn by both players and the outcome. Winning move is displayed with a yellow star.

This self-report questionnaire is based on the Peters et al. Delusions Inventory-21 (PDI-21) (Peters et al 1999) and consists of 42 items measuring the presence of *positive* psychotic experiences (20 items), *negative* psychotic experiences (14 items), and *depressive* experiences (8 items) that an individual may have experienced over the last 12 months (Stefanis et al 2002). The occurrence of these symptoms is reported on a likert frequency scale from 1 (never) to 4 (nearly always), and the associated distress on a scale ranging from 1 (not distressed) to 4 (very distressed). Cronbach's α for this scale in this study is .89, which indicates high internal consistency.

For current purposes, the 20-item CAPE positive scale is used as a measure of psychosis proneness. The assessment of positive symptoms rather than the general construct of psychosis, which comprises both negative and positive symptoms, is based on evidence for autism-positive symptoms axis in the non-clinical population (Dinsdale et al 2013), and that negative symptoms do not reliably discriminate between ASD and SSD (Kastner et al 2015, Searles Quick et al 2015, Spek & Wouters 2010). The internal consistency of this scale in this study is good (Cronbach's $\alpha = .75$), and falls within the range of values reported in other studies within the general population (Lin et al 2011). In the current study, participants had a mean score of 25.28 (Range: 20-32; SD= ± 3.57), which are comparable to scores within a community sample of adolescents (Yung et al 2009) and adults (Abu-Akel et al 2015).

The Autism Spectrum Quotient (AQ) Questionnaire

This self-report questionnaire consists of 50 items that measure the presence of traits associated with the autistic spectrum within the general population (Baron-Cohen et al 2001). Each item is given a score of 0 or 1. Higher scores indicate the presence of greater autistic tendencies. The AQ's internal consistency in this study is good (Cronbach's $\alpha = .81$), and is comparable to the values reported in other studies (Austin 2005). In the current study, participants had a mean score of 15.49 (Range: 3-31; SD= ± 6.65). The association of the AQ with the CAPE positive scale was non-significant ($r=.28$, $p=.19$) (see supplementary Figure 1).

fMRI data acquisition and analysis

Data were acquired in a single scanning session using a 3T Philips Achieva scanner. 176 T2*-weighted standard echo planar imaging (EPI) volumes were obtained in each of the RPS task runs, using a 32 channel head coil. Parameters used to achieve whole brain coverage are as follows: TR=2.5s, TE=35ms, acquisition matrix = 80 x 80, flip angle = 83° , isotropic voxels 3x3x3 mm³, 42 slices axial acquisition obtained consecutively in a bottom-up sequence. Using the same parameters, 71 EPI volumes were acquired for each block of the localizer task. A T1-weighted scan was then acquired as a single volume at higher spatial resolution as a 3D TFE image (matrix size 288x288, 175 slices, sagittally acquired and reconstructed to 1x1x1 mm³ isotropic voxels. TE = 3.8ms; TR = 8.4 ms).

Preprocessing and statistical analyses of the data were performed using the FMRIB software library (FSL version v.5.0.6; FMRIB, Oxford, www.fmrib.ox.ac.uk/fsl). For both experiments, initial preprocessing of the functional data consisted of slice timing correction, and motion

correction (MCFLIRT). The blood oxygen level dependent (BOLD) signals were high-pass filtered using a Gaussian weighted filter to remove low-frequency drifts in the bold signal. Spatial smoothing of the BOLD signal was performed using a 5mm full-width-half-maximum kernel. The functional data were registered to their respective structural images and transformed to a standard template based on the Montreal Neurological Institute (MNI) reference brain, using a 6-DoF linear transformation (FLIRT).

RPS task experiment analysis:

Playing against a computer or a human, with either agency or by following a script, provided the four baseline conditions. These four conditions comprised a 2x2 ANOVA experimental design with factor 1 being the human vs. computer opponent and factor 2 being the element of implied agency from the opponent (active vs. passive). Condition regressors were convolved with the canonical hemodynamic response function within a general linear model framework (GLM). A high-pass filter with a cut-off of 105s was used. Motion parameters were treated as regressors of no interest in order to account for unwanted motion effects. Session data were aggregated per participant using a second level fixed effects model. Third level modelling was used to aggregate the data across participants in a 2x2 repeated measures ANOVA with Active vs. Passive and Human vs. Computer as within subjects factors, employing a mixed effects analysis with cluster based thresholding at $Z > 2.3$, $p_{corr} < 0.05$. An overlap analysis between the thresholded data ($Z > 2.3$, $p_{corr} < 0.05$) for the Human > Computer and the Active > Passive contrasts was then conducted to identify shared activations across the two thresholded contrasts.

Regions of Interest (ROI) analysis:

ROI analysis focused on the rTPJ and the paracingulate cortex since only these two regions were active in both the Active > Passive as well as in the Human > Computer contrasts during the RPS task as revealed by the overlap analysis. Masks for these two regions were generated from the ToM localizer task (Hartwright et al 2012). For each of these ROIs, the mean percentage signal change in each of the four RPS experimental conditions (i.e., the active and passive human as well as active and passive computer) was extracted from the aggregate data of each participant across the five runs (i.e., the 24 second-level models) using FSL Featquery (www.fmrib.ox.ac.uk/fsl/feat5/featquery.html).

Statistical analysis:

To evaluate the association of autism tendencies and psychosis proneness on the hemodynamic response of the region (namely, the paracingulate and the rTPJ and its subdivisions), we utilized Generalized Linear Models, with robust estimator, where the Active vs. Passive and Human vs. Computer were entered as fixed factors, and the participants' standardized Z scores on the AQ, CAPEp and their interaction were entered as covariates. Robust regression guards against violation of statistical assumptions and the undue effects of outliers. Significant interactions were probed using MODPROBE method for SPSS (Hayes & Matthes 2009). The interactions are unpacked by depicting simple regression lines, whereby the effect of one predictor (AQ/CAPEp scores) is examined at the mean (M), one standard deviation below the mean (-1 SD) and one standard deviation above the mean (+1 SD) of the other predictor (CAPEp/AQ scores). These

cut-off points (i.e., M , $-1SD$, $+1SD$) are used here in keeping with the tradition of unpacking interactions using this method. It is noteworthy that this regression procedure does not involve splitting the sample into smaller groups using these cut-off points. Rather, it estimates the effect of a predictor on the dependent variable, while holding constant the other predictor at a discrete point. Accordingly, this approach allows us to infer from the model what the effect of autism tendencies/psychosis proneness on brain activity, in a population with certain expressions of psychosis proneness/autism tendencies.

Results

An overlap analysis between the thresholded data ($Z > 2.3$, $p_{corr} < 0.05$) for the Human > Computer and the Active > Passive contrasts revealed shared activations in the paracingulate cortex and the rTPJ. Masks for these two regions were generated from the Theory of Mind (ToM) Localizer Task (Hartwright et al 2012, Saxe & Kanwisher 2003) (see Figure 2).

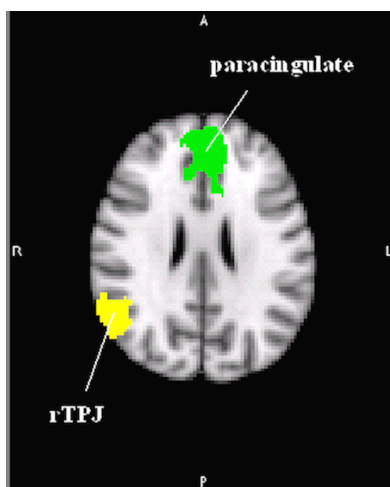


Figure 2. Masks for the overlapping regions between the Human > Computer and the Active > Passive contrasts. Coordinates of the mask for the paracingulate cortex (in green) are $[-4, 50, 20]$ and for the rTPJ (in yellow) are $[58, -52, 28]$.

First, we examined the impact of autism tendencies and psychosis proneness and their interaction on the hemodynamic response of the paracingulate cortex and the rTPJ using Generalized Linear Models as specified above. With respect to the hemodynamic response of the paracingulate cortex, the omnibus test showed that the overall model was non-significant ($\chi^2=9.50$, $df=5$, $p=.091$). However, when the data for the rTPJ were subject to the same analysis, the overall model was significant ($\chi^2=19.51$, $df=5$, $p=.002$, $R^2=.18$). Activity within the rTPJ was negatively associated with AQ scores ($\beta(se)=-.070(.028)$, $df=1$, $\chi^2=6.54$, $p=.011$), and positively with both CAPEp scores ($\beta(se)=.102(.027)$, $df=1$, $\chi^2=13.72$, $p<.001$) and the interaction term ($\beta(se)=.077(.022)$, $df=1$, $\chi^2=11.80$, $p=.001$) (Figure 3). This modulation was observed in the active vs. passive condition ($\chi^2=3.84$, $df=1$, $p=.050$), but not in the human vs. computer condition ($\chi^2=1.48$, $df=1$, $p=.23$) (see Supplementary Table 1).

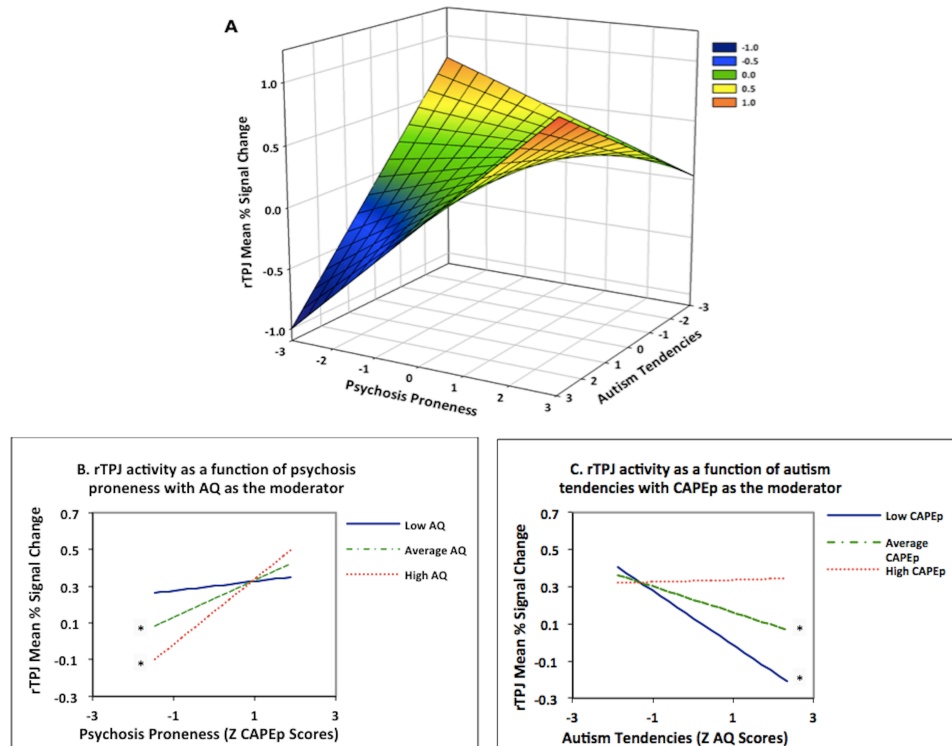


Figure 3. (A) 3-D representation of the interactive effect of autism tendencies and psychosis proneness on mean percent signal change of the rTPJ. (B) Visualizes the association between psychosis and rTPJ activity by plots of simple regression lines with low (-1 SD), average, and high (+1 SD) AQ scores as moderators, showing an increase in the positive effect of psychosis proneness on rTPJ activity with increasing autism tendencies. (C) Visualizes the association between autism tendencies and rTPJ by plots of simple regression lines with low (-1 SD), average, and high CAPEp (+1 SD), showing a decrease in the negative effect of autism tendencies on rTPJ activity with increasing psychosis proneness. Asterisk = p -value < .05.

As can be seen from Figure 3A, rTPJ activity is greater in psychosis-prone individuals compared to autism-prone individuals (see also Supplementary Figure 2A which depicts the raw data of the model presented in Figure 3A). Intriguingly, the rTPJ activates to a similar degree in individuals presenting with high scores as well as in individuals presenting with low scores on both scales. In order to examine if rTPJ activity is modulated by the relative expression of

psychosis vis-à-vis autism, the participants' psychosis bias was calculated by subtracting their z-normalized AQ scores from their z-normalized CAPEp scores. A regression analysis confirmed that the Psychosis-Bias scores positively predicted rTPJ activity ($\beta(\text{se})=.072(.020)$, $df=1$, $\chi^2=13.37$, $p<.001$, $\text{Exp}(\beta)= 1.075$, $R^2=.11$).

Next, we probed the interaction term using the method by Hayes and Matthes (2009) described above. The positive relationship between psychosis proneness and rTPJ activity (Figure 3B) was significant when AQ scores were at the mean ($\beta=0.102$, $p=0.003$) as well as when they were high (+1 SD) ($\beta=0.177$, $p<.001$), but not when they were low (-1 SD) ($\beta=0.026$, $p=0.53$).

Conversely, the negative relationship between autism tendencies and rTPJ activity (Figure 3C) was significant when CAPEp scores were low ($\beta=-0.146$, $p=0.003$) as well as when they were at the mean ($\beta=-0.076$, $p=.038$), but not when they were high ($\beta=0.006$, $p=0.89$). This pattern suggests that activity within the rTPJ is diametrically modulated, such that autism tendencies were associated with decreased activity and psychosis proneness with increased it.

To shed light on the rTPJ debate, we utilized the masks from Mars et al. (2012) to further examine the neural activity of the rdTPJ and rvaTPJ as a function of autism tendencies and psychosis proneness. Note that the rvpTPJ, as defined in Mars et al. (2012), overlaps considerably with the region within which we conducted our analyses in Figure 3 above (see Figure 4B). For this reason, we only ran post-hoc tests on the rdTPJ and the rvaTPJ sub-regions delineated in Mars et al. (2012). In addition, in order to highlight the distinction between the anterior and posterior divisions of the rTPJ, we now refer to *our* rTPJ (from the analysis in Figure

3) the rvpTPJ in the discussion, in order to be consistent with the labeling from Mars et al. (2012).

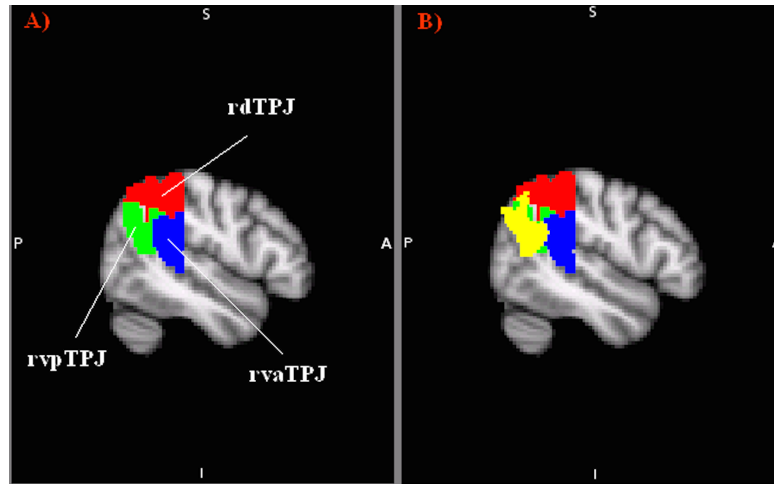


Figure 4. (A) Mars et al.'s (Mars et al 2012) parcellation of the right TPJ into dorsal (center of gravity [49, -46, 46]) (rdTPJ), ventral posterior [54, -55, 26] (rvpTPJ) and ventral anterior [59, -37, 30] (rvaTPJ) subdivisions. Masks were obtained from www.rbmars.dds.nl/CBPatlases.htm. (B) An overlay of the rTPJ (in yellow), defined by the ToM localizer task, over the rTPJ, as delineated by Mars et al., shows that our localized rTPJ [56, -64, 30] significantly matches the rvpTPJ, with minimal overlaps with the rdTPJ and the rvaTPJ. Regions are superimposed on a sagittal section, x=20.

The omnibus test for the rdTPJ was non-significant ($\chi^2=9.44$, $df=5$, $p=.093$), but significant for the rvaTPJ ($\chi^2=16.89$, $df=5$, $p=.005$, $R^2=.16$). Parameter estimates indicated that rvaTPJ activity was negatively associated with CAPEp scores ($\beta(se)=-.052(.018)$, $df=1$, $\chi^2=8.17$, $p=.004$) and positively with the interaction term ($\beta(se)=.073(.015)$, $df=1$, $\chi^2=24.48$, $p<.001$). The association with AQ scores was negative but non-significant ($\beta(se)=-.013(.020)$, $df=1$, $\chi^2=.38$, $p=.54$). Note, that this modulation is not specific to either the active vs. passive condition ($\chi^2=1.56$, $df=1$,

$p=.21$) or the human vs. computer condition ($\chi^2=.14$, $df=1$, $p=.70$) (see Figure 5 and Supplementary Table 2).

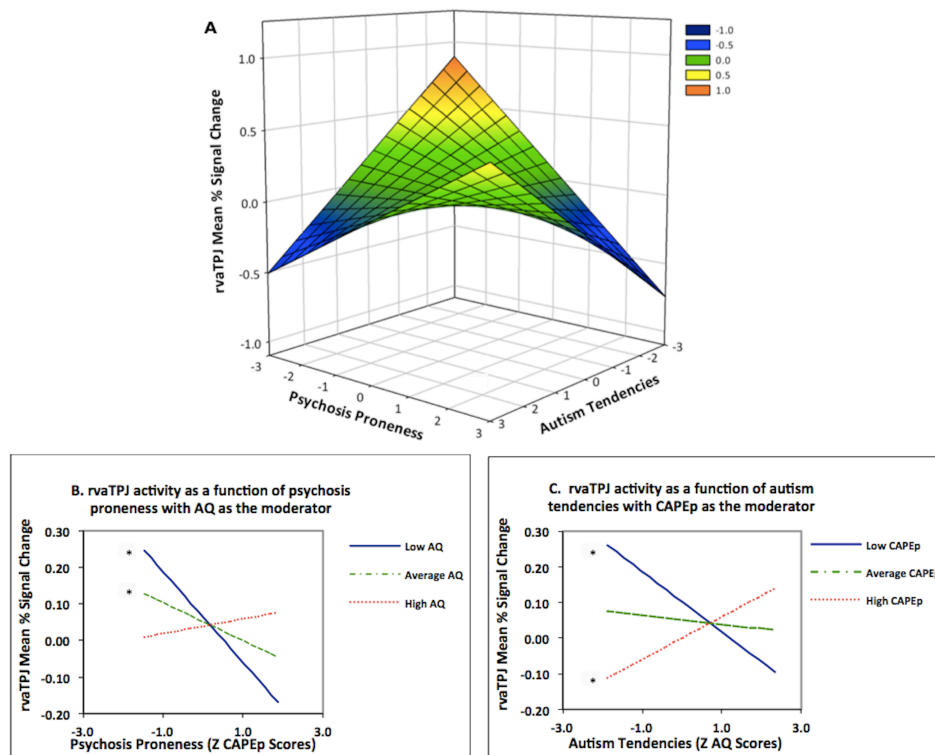


Figure 5. (A) 3-D representation of the interactive effect of autism tendencies, psychosis proneness on mean percent signal change of the rvaTPJ. (B) Visualizes the association between psychosis and rvaTPJ activity by plots of simple regression lines with low (-1 SD), average, and high (+1 SD) AQ scores as moderators, showing a diminishing of the negative effect of psychosis proneness on rvaTPJ activity with increasing autism tendencies. (C) Visualizes the association between autism and rvaTPJ by plots of simple regression lines with low (-1 SD), average, and high CAPEp (+1 SD), showing a reversal of the negative effect of autism tendencies on rvaTPJ activity with increasing psychosis proneness. Asterisk = p -value $<.05$.

In contrast to the pattern of activation we observed in the rvpTPJ (Figure 3A), Figure 5A shows that autism-prone individuals compared to psychosis-prone individuals tend to have higher rvaTPJ activity (Supplementary Figure 2B depicts the raw data of the model presented in Figure

5A). Intriguingly, here too, we see that the rvaTPJ activates to somewhat a similar degree in individuals scoring high as well as in individuals scoring low on both scales. In contrast to the rvpTPJ, where the Psychosis-Bias scores were positively associated with activity, a regression analysis controlling for rvpTPJ activity revealed that the Psychosis-Bias scores were negatively associated with rvaTPJ activity ($\beta(\text{se}) = -.056(.018)$, $df=1$, $\chi^2=9.26$, $p=.002$, $\text{Exp}(\beta) = .946$, $R^2=.09$).

Furthermore, when probing the interaction between AQ and CAPEp scores, the positive relationship between psychosis proneness and rvaTPJ activity (Figure 5B) was significant when AQ scores were low ($\beta=-0.124$, $p<0.001$) as well as when AQ scores were at the mean ($\beta=-0.052$, $p=.048$), but non-significant when they were high ($\beta=0.020$, $p=0.50$). Conversely, there was a negative relationship between autism tendencies and rvaTPJ activity (Figure 5C) when CAPEp scores were low ($\beta=-0.084$, $p=0.030$), none at the mean ($\beta=-0.012$, $p=.64$), and trending towards a positive relationship when CAPEp scores were high ($\beta=0.060$, $p=0.063$), but which becomes significant ($p<.05$) in individuals scoring above a Z value of 1.056 (which roughly corresponds to a score of 29 on the CAPEp scale). This pattern suggests that activity within the rvaTPJ is also diametrically modulated by autism tendencies and psychosis proneness, but in different, and largely opposite pattern when compared to the rvpTPJ (Figure 3).

Discussion

In this study, we examined the effect of co-occurring autism tendencies and psychosis proneness on the neural activity of core regions within the mentalizing network of neurotypical adults while performing a social competitive game. The results indicated that autism tendencies

and psychosis proneness have diametric influences on the neural activity within the ventral posterior (mentalizing) and anterior (attention-reorienting) subdivisions of the rTPJ. Specifically, while autism tendencies were associated with decreased activity in the ventral posterior rTPJ, psychosis proneness was associated with increased activity. Intriguingly, this pattern was reversed for the ventral anterior subdivision of the rTPJ, such that activity was positively associated with autism tendencies and negatively with psychosis proneness. Contrary to our expectations, task-related activations within the paracingulate cortex were unrelated to inter-individual differences in autism tendencies or psychosis proneness. While this null finding may simply be due to not having sufficient power, an intriguing possibility for future research is to examine whether autism and psychosis expressions affect activity of posterior regions within the mentalizing network, which are involved in the representation of mental states, differently than anterior regions, which are more involved in the application and deployment of represented mental states (Abu-Akel & Shamay-Tsoory 2011).

The nature of the interactive effect of autism and psychosis expressions on rTPJ activity is consistent with the diametric model positing that autism and schizophrenia spectrum disorders are etiologically and phenotypically diametrical exerting opposing influences on activity and behavior (Abu-Akel & Bailey 2000, Abu-Akel et al 2015, Crespi & Badcock 2008, Crespi et al 2010). We propose that the diametric modulation of the rvpTPJ might be reflective of the neural effort to balance the tendency of psychosis to lead to overmentalizing and autism to undermentalizing (Abu-Akel & Bailey 2000, Bara et al 2011, Crespi & Badcock 2008, Crespi et al 2010). Indeed, several mentalizing studies associated overactive rTPJ activity with

overmentalizing in schizophrenia spectrum disorders (Backasch et al 2013, Ciaramidaro et al 2015, Walter et al 2009), and contrastingly an underactive rTPJ with undermentalizing in autism spectrum disorders (Ciaramidaro et al 2015, Kana et al 2015, Lombardo et al 2011).

This neural pattern was not observed in all studies, however. For example, hypo-activation was observed in the rTPJ of schizophrenia patients compared to controls (Lee et al 2011), and no differences were observed between low versus high psychosis-prone groups (Modinos et al 2010, van der Meer et al 2013). However, dividing the participants into low and high groups is not amenable to assessing the effect of individual differences on the degree of neural activation. It is also unknown the extent to which unmeasured autism expressions might have influenced these results. Similarly, ASD studies also reported positive association between AQ scores and rTPJ activity (Nummenmaa et al 2012, von dem Hagen et al 2011). However, the positive correlation found in the Nummenmaa et al. study was during an attentional/gaze perception task, and that of the von dem Hagen et al. study was in a region whose coordinates [52, -42, 12] fall within the rvaTPJ. It is noteworthy that the AQ scores in the Nummenmaa et al. study also correlated positively with the supramarginal gyrus, which constitutes part of the rvaTPJ as defined in our study. As such, the results reported in Nummenmaa et al. (2012) and von dem Hagen et al. (2011) are consistent with our current finding showing that activity in the attentional rvaTPJ is positively associated with autism tendencies.

Similarly, we propose that the diametric modulation of autism tendencies and psychosis proneness of the rvaTPJ (Figure 5) appears to reflect the neural effort to balance the inability to

filter unimportant and distracting information associated with psychosis and the tendency for increased focus of attention associated with autism. This interpretation is consistent with findings showing that deactivation in this region reflects the filtering of irrelevant and distracting information, and that such deactivation ceases once a target has been detected (Shulman et al 2007). Although attention re-orienting was not measured behaviorally in our study, we tested whether the autism-related up-regulation of the rvaTPJ might reflect increased focus of attention. A regression analysis showed that activity of the rvaTPJ was positively associated with the attention-switching subscale of the AQ questionnaire, where higher scores reflect stronger focus of attention ($\beta(\text{se})=.069(.024)$, $\chi^2=8.19$, $df=1$, $p=.004$) (see Supplementary Table 3). This finding is consistent with Nummenmaa et al. (2012) who also reported positive association between the attention-switching subscale and rTPJ activity while performing an attentional/gaze perception task. It is important to note that the attention-switching subscale was not associated with rvpTPJ activity ($\chi^2=0.06$, $df=1$, $p=.81$).

Taken together, we hypothesize that higher psychosis-proneness leads to an increase in the availability of information due to reduced information filtering (reflected in deactivation in rvaTPJ) and consequently greater effort when trying to mentalize with this information (reflected in greater rvpTPJ activity). These consequences of psychosis-proneness are countered by the relative expression of the autistic trait associated with attentional focus, which restricts the amount of information available for mentalizing in the rvpTPJ. This interpretation is consistent with the opposing domains hypothesis positing reciprocal interaction between regions involved in social cognition and regions involved in attentional processing (Jack et al

2012, Kubit & Jack 2013). Future research can test this hypothesis by examining performance on attentional and mentalizing paradigms following stimulation of key regions within the attentional and mentalizing networks in individuals with varying degrees of autism and psychosis expressions.

Based on the strong interactive effect between autism and psychosis expressions in the rTPJ, we suggest that such inter-individual variation within and across disorders can be accounted for in terms of the relative expression of one disorder vis-à-vis the other. However, given that our findings are based on the relative expression of autism and psychosis traits among neurotypical adults, a further critical step is to examine whether these findings generalize to their respective clinical entities. Nonetheless, the impact of these sub-threshold clinical traits on neural functioning in a manner similar to what has been observed in patients with these disorders suggests that neural abnormalities are not necessarily a consequence of the disorders. This also raises the possibility that an important difference between patients and non-patients is in the relative expression of autism and psychosis traits. Our findings thus provide a framework that could reconcile discrepant results such that hypo- or hyper-activation in either disorder (Ciaramidaro et al 2015, Lee et al 2011, Sugranyes et al 2011) may be due to failure to capture the diametric influence of the other disorder. Additionally, the effect of individual differences in autism and psychosis expressions in neurotypicals on neural activity raises concerns regarding hitherto findings reported in studies comparing clinical and non-clinical groups (Brunet et al 2003, Modinos et al 2010, van der Meer et al 2013). Might differences (or lack thereof) between clinical and healthy controls be confounded by the relative expression of autism and

psychosis in 'healthy' controls? That is, it is reasonable to assume that the extent of the difference between the healthy and the clinical populations is a function of the extent of subclinical expressions in the healthy group. This should be of particular concern when the distribution of traits in the healthy sample is skewed.

Our findings may also have implications in relation to the wider social brain/mentalizing network. We suggest that a fuller understanding of its functionality requires an examination of the extent to which it is interactively linked with regions that are responsible with domain general processing. This is particularly important for research concerned with understanding the causal links between regions responsible for higher level social cognitive processing and regions associated with domain-general attentional processes. In this regard, delineation of the causal links among subdivisions within the TPJ would be an important step forward in understanding their role within the mentalizing network. Furthermore, the opposite effects of autism and psychosis on neural activity within the TPJ suggest that these conditions influence independent yet interacting systems, which may be precipitated by discrete genetic mechanisms (Crespi & Badcock 2008, Crespi et al 2010). Answering this question requires research that examines the effect of autism and/or psychosis genetic risk factors with clear links to the development and functionality of brain regions within the mentalizing network. This could build on existing research showing, for example, that the zinc finger protein 804A (*ZNF804A*) single nucleotide polymorphisms (SNPs), which confer risk for both autism and schizophrenia (Anitha et al 2014), affect brain activations within the mentalizing network in a dose-dependent manner (Walter et al 2011).

Our study is the first to show that the postulated diametric modulation of autism tendencies and psychosis proneness on behavior and performance are detectable at the neural level in a region that is a core component of social functioning (Chien et al 2015, Lombardo et al 2011). The association of the neural response in the socio-cognitive and attention-reorienting networks with the extended autism and psychosis spectra in the neurotypical population further suggests that the assessment of both spectra in the “control group” could have important consequences for establishing baseline measures for the assessment of behavior and brain phenotypes in the clinical groups. Furthermore, the contrastive modulation of the ventral anterior versus the posterior rTPJ underscores the distinct functionality of these subdivisions (Corbetta et al 2008, Mars et al 2012, Scholz et al 2009), and provides an insight for the debate surrounding the functional link between regions responsible for higher level social cognitive processing and regions associated with domain-general attentional processes.

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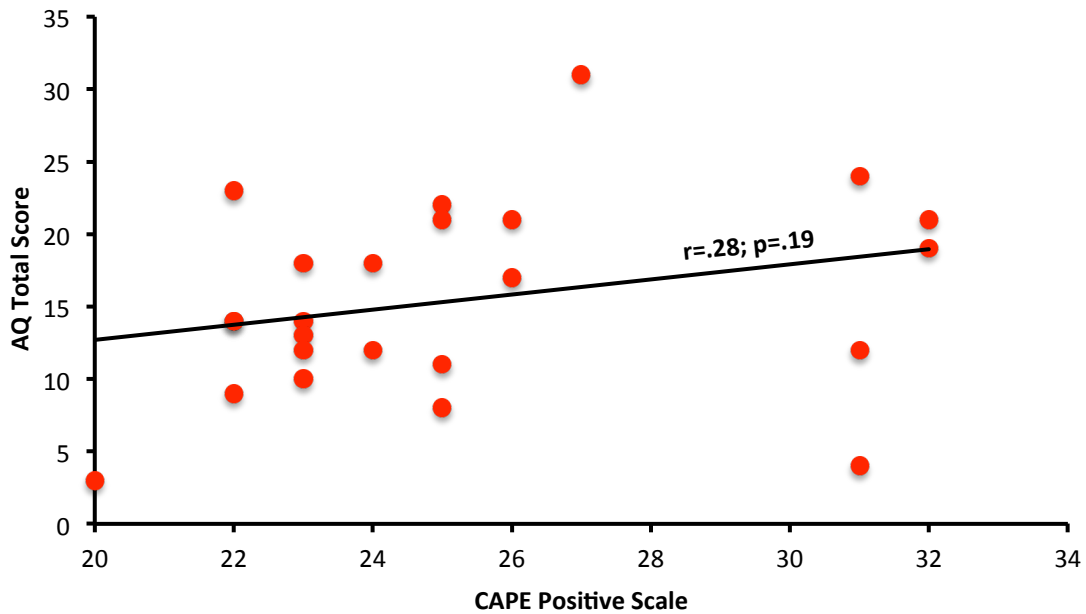
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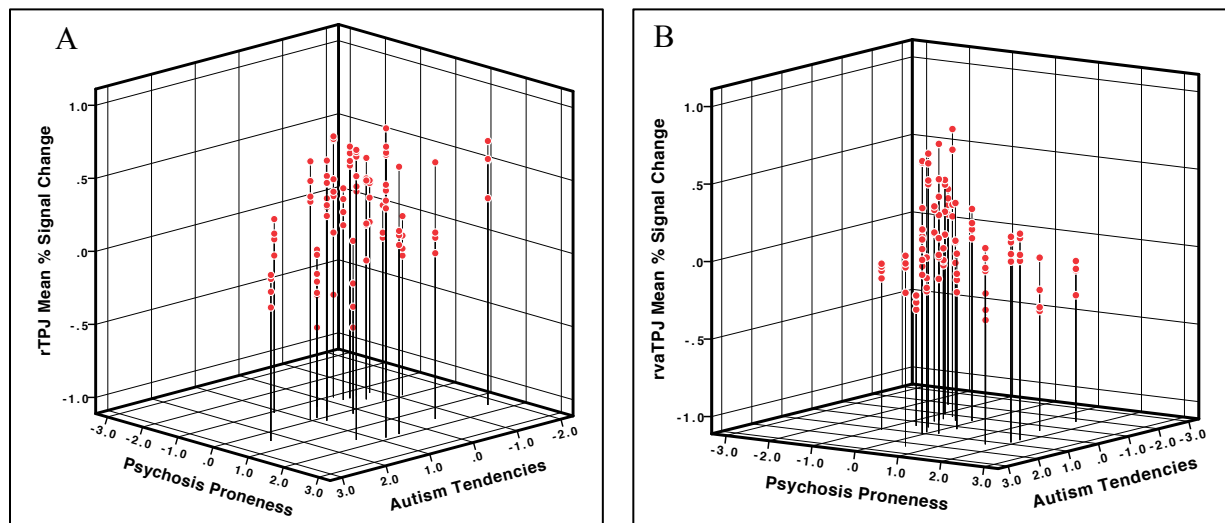
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Supplementary Information



Supplementary Figure 1. A scatter plot depicting the association between the Autism Spectrum Quotient Scale (AQ) scores and the scores on the Positive scale of the Community Assessment of Psychic Experiences (CAPE positive scale, CAPEp).



Supplementary Figure 2. A 3-D scatter plot depicting, across all conditions, the association between psychosis proneness and autism tendencies with % signal change of the rTPJ (corresponding to Mars et al. (2012) rvpTPJ) (**Panel A**) and the rvaTPJ (**Panel B**).

Supplementary Table 1. Summary of coefficients with mean percent signal change of the rTPJ (=rvpTPJ) as the dependent variable.

Model Coefficient	β	(SE)	Waldχ^2	df	Exp(β)	Sig.
Constant	.209	.055	14.70	1	1.233	<.001
AP	.115	.059	3.84	1	1.122	=.050
HC	-.071	.059	1.48	1	.931	=.225
AQ	-.070	.028	6.54	1	.932	=.011
CAPEp	.102	.027	13.72	1	1.107	<.001
AQxCAPEp	.077	.022	11.80	1	1.080	=.001

AP= Active-Passive; HC= Human-Computer; AQ= Autism Quotient; CAPEp= Positive scale of the Community Assessment of Psychic Experiences.

Supplementary Table 2. Summary of coefficients with mean percent signal change of the rvaTPJ as the dependent variable.

Model Coefficient	β	(SE)	Waldχ^2	df	Exp(β)	Sig.
Constant	.031	.041	.58	1	1.03	=.45
AP	.058	.047	1.56	1	1.06	=.21
HC	-.018	.047	.14	1	1	=.70
AQ	-.013	.020	.38	1	.99	=.54
CAPEp	-.052	.018	8.18	1	.95	=.004
AQxCAPEp	.073	.015	24.48	1	1.08	<.001

AP= Active-Passive; HC= Human-Computer; AQ= Autism Quotient; CAPEp= Positive scale of the Community Assessment of Psychic Experiences.

Supplementary Table 3. Summary of coefficients with mean percent signal change of the rvaTPJ as the dependent variable with the attention-switching subscale of the AQ as a covariate, controlling for CAPEp scores.

Model* Coefficient	β	(SE)	Waldχ^2	df	Exp(β)	Sig.
Constant	.051	.041	1.53	1	1.05	=.22
AP	.058	.047	1.53	1	1.06	=.22
HC	-.018	.047	.14	1	0.98	=.71
Attention-Switching	.069	.024	8.19	1	1.07	=.004

* Coefficients are estimates of a Generalized linear model ($\chi^2=15.17$, $df=4$, $p=.004$, $R^2=.15$), where the Active vs. Passive (AP) and Human vs. Computer (HC) were entered as fixed factors, and the participants' standardized Z scores of the attention-switching subscale of the AQ as a covariate. Higher scores on the attention-switching subscale reflect poor attention-switching or strong focus of attention.